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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte STEPHEN C. SUFFIN, W. HAMLIN EMORY, and
LEONARD BRANDT,
Appellants[1]

Appeal 2010-000313
Application 10/697,497
Technology Center 1600

Before ERIC GRIMES, CAROL A. SPIEGEL, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL[2]

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[1] The real party in interest is Central Nervous System Response, Inc. (Supplemental Appeal Brief filed 22 April 2009 ("App. Br.") at 3). This decision also cites to the Examiner's Answer mailed 6 July 2009 ("Ans."), and the Reply Brief filed 4 September 2009 ("Reply Br.").

[2] The two-month period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

Appellants appeal under 35 U.S.C. § 134 from an Examiner's final rejection of claims 1-3. Claims 4-16, the only other pending claims, are withdrawn from consideration as directed to a non-elected invention. (App. Br. 3; Ans. 2.) We have jurisdiction under 35 U.S.C. § 134. We AFFIRM.

I. Statement of the Case

Claim 1 is illustrative and reads (App. Br. Claims App'x i):

> A formulation comprising, oxcarbazepine and an antidepressant, wherein said antidepressant is selected from the group consisting of bupropion and bupropion metabolites.

The Examiner rejected claims 1-3 under 35 U.S.C. § 103(a) as obvious over Quessy[3] and Zakrzewska[4] (Ans. 3-5).

The Examiner found that Quessy teaches a formulation comprising bupropion and sodium channel blockers, including oxcarbazepine and lamotrigine, useful for treating neuropathic pain (*id.* at 3). The Examiner also found that Zakrzewska teaches that oxcarbazepine is an antineuralgic that is effective in controlling pain in intractable trigeminal neuralgia without adverse side effects (*id.* at 4). The Examiner concluded that it would have been obvious to combine bupropion with oxcarbazepine into an antineuralgic pain formulation based on the combined teachings of Quessy and Zakrzewska (*id.*).

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[3] U.S. Patent Application Publication 2002/0147196 A1, *Composition and Method for Treating Neuropathic Pain*, published 10 October 2002, Quessy et al. ("Quessy").

[4] JM Zakrzewska and PN Patsalos, *Oxcarbazepine: a new drug in the management of intractable trigeminal neuralgia*, 52 JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY 472-476 (1989) ("Zakrzewska").

Appellants essentially argue that "[a]s lamotrigine and oxcarbazepine are not structurally similar, it would not be expected that they have the same therapeutic efficacy" (App. Br. 6, footnote omitted) and, therefore, there is no proper motivation to combine Quessy and Zakrzewska (*id.* at 7). Appellants rely on a Jensen abstract,[5] a Tremont-Lukats abstract,[6] and two Declarations by co-inventor Stephen Suffin (Suffin Decl. I[7] and Suffin Decl. II[8]) in support of their position.

Appellants state that claims 2 and 3 stand or fall with claim 1 (App. Br. 12). Thus, we decide this appeal on the basis of claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

At issue is whether the evidence of record supports a conclusion that it would have been *prima facie* obvious to combine bupropion and oxcarbazepine in an antineuralgic pain formulation; and, if so, whether Appellants have provided evidence that, when weighed with the evidence of obviousness, is sufficient to overcome the *prima facie* conclusion of obviousness.

II. Findings of Fact

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

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[5] TS Jensen and NB Finnerup, *Management of neuropathic pain*, 1 CURRENT OPINIONS IN SUPPORTIVE PALLIATIVE CARE 126-131 (August 2007), abstract only supplied ("Jensen abstract").

[6] Tremont-Lukats et al., *Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy*, 60 DRUGS 1029-1052 (November 2000), abstract only supplied ("Tremont-Lukats abstract").

[7] Declaration of Dr. Stephen Suffin under 37 C.F.R. § 1.132, dated 20 July 2007 ("Suffin Decl. I").

[8] Second Declaration of Dr. Stephen Suffin under 37 C.F.R. § 1.132, dated 31 October 2007 ("Suffin Decl. II").

A. Quessy

[1] Quessy discloses compositions and methods for alleviating neuropathic pain (Quessy ¶ 1).

[2] The composition of Quessy

> comprises (1) a compound that inhibits the reuptake of both norepinephrine and dopamine (NE-DA reuptake inhibitor) or inhibits the reuptake of norepinephrine (NE reuptake inhibitor), or a pharmaceutically acceptable derivative thereof, in combination with (2) a compound that acts as a sodium channel blocker …, or a pharmaceutically acceptable derivative thereof … [T]he combination manifests synergism in at least one of the following: greater efficacy as measured by lower pain scores; efficacy in a greater number of patients; equivalent efficacy with the combination using lower doses of each agent; faster onset of action with the combination; lower incidence of undesirable side effects; fewer patients using additional medications to relieve symptoms, and/or longer lasting pain relief. [*Id.* at ¶ 9.]

[3] Quessy explicitly identifies and claims bupropion as an NE-DA reuptake inhibitor and lamotrigine and oxcarbazepine as sodium channel blockers (*id.* at ¶¶ 10-11; claims 1-3).

[4] Example 3 of Quessy demonstrates a synergistic combination of lamotrigine and bupropion for treating neuropathic pain based on greater efficacy against neuropathy hypersensitivity, efficacy in a greater number of subjects, equivalent efficacy with the combination using lower doses of each agent, faster onset of action with the combination, or longer lasting pain relief (*id.* at ¶¶ 46-52).

B. Zakrzewska

[5] Zakrzewska teaches that "oxcarbazepine has potent antineuralgic properties in the absence of significant side effects and therefore may be useful in the management of intractable trigeminal neuralgia" (Zakrzewska abstract; 475, last ¶).

C. Appellants' rebuttal evidence

[6] The Jensen abstract, published after the instant filing date, states that

> [r]andomized controlled trials have consistently shown efficacy of tricyclic antidepressants, gabapentin/pregabalin, opioids, tramadol, and serotonin and noradrenaline-reuptake inhibitors for the treatment of various neuropathic pain conditions, lidocaine patches for postherpetic neuralgia and cannabinoids for pain in multiple sclerosis. Carbamazepine or oxcarbazepine is the treatment of choice for trigeminal neuralgia. The efficacy of these drugs in other neuropathic pain conditions as well as the efficacy of lamotrigine and topical capsaicin is questionable, but they may be useful in a subgroup of patients.
> SUMMARY: For each patient, considerations on the underlying pain mechanisms, immediate and potential long-term side effects, and price as well as comorbidities and concurrent medications will decide which drug should be the first choice, but until further progress is made towards a mechanism-based classification, treatment is likely to be a trial-and-error process where drug combinations may also be considered.

[7] The Tremont-Lukats abstract, published prior to the instant filing date, states that

> [n]europathic pain … is a formidable therapeutic challenge to clinicians … Basic research … has shown that a number of pathophysiological and

> biochemical changes take place in the nervous system as a result of an insult. This property of the nervous system to adapt morphologically and functionally to external stimuli is known as neuroplasticity and plays a crucial role in the onset and maintenance of pain symptoms. Many similarities between the pathophysiological phenomena observed in some epilepsy models and in neuropathic pain models justify the rational [sic] for use of anticonvulsant drugs in the symptomatic management of neuropathic pain disorders. Carbamazepine … probably alleviates pain by decreasing conductance in Na+ channels ... Results from clinical trials have been positive in the treatment of trigeminal neuralgia, painful diabetic neuropathy and postherpetic neuralgia. The availability of newer anticonvulsants … has marked a new era in the treatment of neuropathic pain. …[G]abapentin should be considered the first choice of therapy for neuropathic pain. Evidence for the efficacy of phenytoin as an antinociceptive agent is … weak to modest. Lamotrigine has a good potential to modulate and control neuropathic pain …. There is potential for phenobarbital, clonazepam, valproic acid, topiramate, pregabalin and tiagabine to have antihyperalgesic and antinociceptive activities based on result[s] in animal models of neuropathic pain, but the efficacy of these drugs in the treatment of human neuropathic pain has not yet been fully determined in clinical trials. The role of anticonvulsant drugs in the treatment of neuropathic pain is evolving and has been clearly demonstrated with gabapentin and carbamazepine. Further advances in our understanding of the mechanisms underlying neuropathic pain syndromes and well-designed clinical trials should further the opportunities to establish the role of anticonvulsants in the treatment of neuropathic pain.

[8] Coinventor Stephen Suffin, M.D. (Suffin Decls. I and II, ¶¶ 1-2) testified that "[m]any drugs have multiple mechanisms of action" (Suffin Decl. II, ¶ 8).

[9] Dr. Suffin testified that the rEEG multivariant measurement data provided in his declarations show that lamotrigine and oxcarbazepine, alone or in combination with bupropion produce different patient response distribution patterns (Suffin Decl. I, ¶¶ 4-5, Suffin Decl. II, ¶¶ 4-7).

[10] Specifically, Dr. Suffin testified that the provided data show that lamotrigine and oxcarbazepine, alone or in combination with bupropion, produce a "stimulant drug" response and a "depressant drug" response, respectively (Suffin Decl. I, ¶¶ 4-6; Tables 1 and 2; Suffin Decl. II, ¶¶ 5-7).

[11] Dr. Suffin concluded that "these data show that lamotrigine and oxcarbazepine are not interchangeable simply because they have been suggested to have a mechanism of action in common (i.e., for example, sodium channel inhibition)" (Suffin Decl. I, ¶ 7).

III. Discussion

A. Legal principle

An invention is obvious if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious . . . to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. The factual inquiries underlying obviousness include (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3)

the level of ordinary skill in the art at the time the invention was made, and (4) any objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). In determining whether obviousness is established by combining the teachings of the prior art, "the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

When the PTO shows *prima facie* obviousness, the burden then shifts to the application to rebut. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). Rebuttal may take the form of "a comparison of test data showing that the claimed compositions possess unexpectedly improved properties … that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument … that is pertinent." *Id.* at 692-93 (citations omitted).

B. Analysis

Here, Quessy provides a virtual roadmap to the claimed formulation not only by disclosing a generic antineuralgic pain formulation comprising an NE-DA reuptake inhibitor in combination with a sodium channel blocker (FF 2), but also by explicitly identifying bupropion and oxcarbazepine as an appropriate NE-DA reuptake inhibitor and sodium channel blocker in particular (FF 3). Zakrzewska provides additional motivation to select oxcarbazepine as the sodium channel blocker in Quessy's formulation by teaching that "oxcarbazepine has potent antineuralgic properties in the absence of significant side effects and therefore may be useful in the

management of intractable trigeminal neuralgia," in particular (FF 5). Therefore, we agree with the Examiner that the subject matter of claim 1 is *prima facie* obvious over Quessy and Zakrzewska.

Appellants essentially argue that the sodium channel blockers disclosed by Quessy, specifically lamotrigine and oxcarbazepine, do not have similar chemical structures and, therefore, would not have been expected to have similar efficacies (App. Br. 5-6). However, the Examiner's *prima facie* conclusion of obviousness is not based on structural homology. The Examiner's rejection is based on Quessy's teaching of combining bupropion with a sodium channel blocker, e.g., oxcarbazepine or lamotrigine, to treat neuropathic pain (FF 1-3) and Zakrzewska's teaching of the significant absence of side effects with oxcarbazepine (FF 5). Therefore, Appellants' rebuttal evidence is insufficient to overcome the Examiner's *prima facie* conclusion of obviousness. For example, none of Appellants' rebuttal evidence refutes Quessy's teaching that a combination of bupropion and oxcarbazepine is efficacious in treating neuropathic pain or that the specific combination claimed provides unexpectedly improved results over the expected synergy, e.g., as shown by bupropion and lamotrigine in Example 3 of Quessy (FF 4). *Dillon*, 919 F.2d at 692-93. Indeed, Dr. Suffin testified that many drugs have multiple mechanisms of action (FF 8).

C. Conclusion

Therefore, we sustain the rejection of claim 1 and, consequently, of claims 2 and 3 under § 103 over Quessy and Zakrzewska. The evidence of record supports a conclusion that it would have been *prima facie* obvious to combine bupropion and oxcarbazepine in an antineuralgic pain formulation; and Appellants' rebuttal evidence, when weighed with the evidence of

obviousness, is insufficient to overcome the *prima facie* conclusion of obviousness.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner to reject claims 1-3 as unpatentable under 35 U.S.C. § 103(a) over Quessy in view of Zakrzewska is AFFIRMED; and,

FURTHER ORDERED that no period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

cdc

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